REMARKS

The claims are not obvious under 35 USC §103

1. Claims 1-4, 6-16, 18-26, 28-31 and 33-35 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the Bankneider *et al.* (U.S. Patent No. 4,751,243) in light of the York et al. (U.S. Patent No. 4,600,717) and DiPiro et al. (Pharmacotherapy, A Pathophysiologic Approad, 2nd ed., Elseview Pub). Applicants respectfully traverse the rejections made by the Patent Office. Applicants respectfully contend that the cited art, taken alone or in combination, does not render claims as currently presented obvious.

Preliminarily, Applicants note that one underlying basis for the Office's persistence in applying the cited art is the statement that "the claims are directed to methods of identifying a compound for treatment of wounds to dermis or epidermis of external body surface in a diabetic animal, which also includes ophthalmic wounds." Applicants respectfully contend that the prior art of record is to the contrary.

First, the DiPiro reference cited by the Office distinguishes dermis/epidermis and ocular tissue. On page 41 of the reference, skin is described as comprising three layers: stratum corneum, epidermis and dermis. The eye, the reference informs the reader on pages 43-44, "with its unique structure and function," is described as being protected by the sclera and cornea. The cornea, as set forth on page 45, is "a unique biological barrier consisting of a thick aqueous stroma sandwiched between the lipid epithelium and endothelium layers." Thus, the very reference cited by the Office contradicts the underlying premise behind the asserted obviousness rejections.

Moreover, another reference cited by the Office in support of the asserted obviousness rejection contains information that supports the non-obviousness of the pending claims. At column 1, lines 13-42, U.S. Patent 4,600,717 to York states:

> While applicant is bound by no theory, it appears that the mechanism of wound healing is related to the mechanism of aldose reductase inhibition and the role of that event in mediating the effects of diabetes. Thus, the method and compositions of the present invention are directed to diabetic individuals. In diabetes there is a condition of high glucose or hyperglycemia. When glucose levels are high, an enzyme called aldose reductase converts glucose to sorbitol at the expense of NADPH. The accumulation of a polyol, such as sorbitol within cells causes pathological changes to those cells and in the tissues comprising those cells. These sickened cells or tissues are not capable of effecting a normal physiological response associated with wound

healing (e.g., effecting normal cell migration and division). ***This corneal epithelium and endothelium of the eye contains aldose reductase. In diabetics the rate of cornea wound healing is retarded significantly.*** On occasion, vision impairing and painful corneal ulceration and scaring results from retarded or abnormal corneal wound healing in the diabetic. The aldose reductase inhibitors inhibit the enzyme aldose reductase within the cornea and thereby promote wound healing in the diabetic. These aldose reductase inhibitors can be applied topically to the eye or systemically to the diabetic to promote wound healing when indicated. While the present disclosure is premised on the above reasonings, the instant compositions and methods of the present invention are not restricted to the diabetic syndrome. (***Emphasis added***)

Thus, the skilled worker might recognize that the eye was a particularly relevant target for aldose reductase inhibitors. There is no evidence of record that the dermis or epidermis expresses aldose reductase or would otherwise be a likely tissue where an aldose reductase inhibitor would promote wound healing.

Applicants respectfully contend that the combination of these teachings would lead the skilled worker away from the claimed invention, by identifying with particularity that the eye is an appropriate target for treatment with an aldose reductase inhibitor (since tissues in the eye express aldose reductase) and that the composition of ocular tissues is different from and indeed "unique" when compared with dermis or epidermis of skin.

Applicants respectfully contend that these distinctions, drawn from the art cited against the pending claims, clearly establishes that the claimed invention is non-obvious. However, to provide a complete response to the Office Action, Applicants turn now to the substance of the grounds of rejection set forth in the Action.

> *According to MPEP, Section 2142, paragraph 3, "To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references to combine reference teachings. Second, there must be reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all claim limitations. The teaching or suggestion to make the claimed combination and reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure."*

Applicants respectfully submit that Bankneider *et al.*, alone or in combination with York et al. and DiPiro et al., does not provide motivation or suggestion to one of skill in the art to perform

instantly submitted method to identify a compound that improves wound healing in diabetic patients. Bankneider *et al.* teaches a method of systemically treating wounds with tolrestat by either oral or parenteral administration. There is no indication in the Bankneider reference that treatment can be accomplished by topical administration. There is a significant, art-recognized difference between the topical treatment and systemic treatment of wounds in terms of delivery, carriers, dosage, efficacy, and toxicity. It is know in the art that certain drugs that are suitable for oral administration might be unsuitable for topical administration, and *vice versa*. Bankneider *et al.* contains no teachings to compensate for these distinctions, and is limited solely to systemic administration. Hence, one of skill in the art could not have a reasonable expectation of success from the teachings of Bankneider *et al.*

This scientific gap between what is taught (or couldn't be predicted from the teachings) in Bankneider *et al.*, systemic administration, and what is claimed in current application, topical administration, is still not bridged by the teaching of York *et al.* York *et al.* teaches the use of aldose reductase inhibitors for treating wounds of the eye topically but such optical topical administration is recognized as being significantly different from topical administration on skin as recited in the currently amended claims. Due to this significant difference in the mode of administration, one of skill in the art will not be able to predict success of method using topical administration of compound without further experimentation. Moreover, the Patent Office has cited no reference that teaches that the treatments specific for eye could be useful in topical administration to skin. The combination of teachings from Bankneider *et al.* and *York et al.* with teachings of DiPiro et al. (that teaches generically the preparation of topical or ophthalmic formulations) also does not provide a reasonable expectation of success of currently claimed method to identify compounds that improves wound healing with all its limitations. Indeed, as set forth above the very distinctions drawn in the DiPiro reference between transdermal and ophthalmic administration would teach away from the claimed invention to one of skill in the art.

2. Claims 1-4, 6-16, 18-26, 28-31 and 33-35 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the York *et al.* (U.S. Patent No. 4,600,717) in view of FDA Guideline No. 38, Chen et al. (U.S. Patent No. 6,232,341) and DiPiro et al. (Pharmacotherapy, A Pathophysiologic Approad, 2nd ed., Elseview Pub). Applicants respectfully traverse the rejections made by the Patent Office based on the arguments presented earlier.

The combination of the Chen reference to the references discussed above does not cure the deficiencies noted above. The Chen *et al*. reference specifically adds nothing more to the knowledge contained in the York reference. Chen merely shows that animal models are used for testing compounds for healing, and simply acts as an example to the utilization of FDA Guideline No 38. (that provides guideline for comparing efficacy of test compositions for treatment of animals against other known or potentially useful agents.)

The Patent Office asserts that there is sufficient motivation or suggestion to combine the references from the knowledge generally available to one of ordinary skill in the art. Applicants note that this formulation is lacking in the specificity required to properly support an obviousness determination. Without further support, the Action states that it is within the level of one of skill in the art to prepare topical or ophthalmic formulation once a desired active agent is known. Applicants respectfully point out that Applicants claim a method for identifying compounds to improve wound healing. The knowledge of one of ordinary skill in the art regarding preparing formulations does not render the claimed method obvious. In fact, knowledge in the art relating to formulations does not provide any predictability that any such formulation would improve wound healing as claimed. Thus, knowledge of a formulation or its active ingredient does not provide a reasonable expectation of success for a method to improve wound healing, and therefore does not render the claimed methods obvious.

Applicants respectfully contend that the cited art, taken alone or in combination, contains no teaching, suggestion or motivation to use the claimed method to identify aldose reductase inhibitors which improve wound healing in a diabetic animal, nor to use the compounds identified by the claimed method to treat skin wounds in a diabetic animal. Applicants further respectfully contend that the cited prior art, properly limited to what it does and does not teach, does not support rejection of any of the rejected claims under 35 U.S.C. §103(a).

CONCLUSION

It is believed that all requirements of patentability are fully met, and allowance of the claims is respectfully requested. If the Examiner believes it to be helpful, the Examiner is invited to contact the undersigned attorney by telephone at 312-913-0001.

Respectfully submitted,

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Date: October 10, 2006

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